IN THE CLAIMS:

1. (amended) A method of reducing ß-cell dysfunction comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1ß into a ß-cell whereby expression of said nucleic acid molecule results in a reduction in ß-cell dysfunction.

5. (amended) A method for reducing Fas mediated ß-cell apoptosis comprising introducing a nucleic acid molecule encoding an inhibitor of Fas mediated apoptosis into a ß-cell whereby expression of said nucleic acid molecule results in a reduction in ß-cell dysfunction.

REMARKS

Claims 1-12 and 20-30 are rejected under 35 U.S.C. §112, first paragraph, and claims 20 and 25 are rejected under 35 U.S.C. §103(a). For reasons set forth in detail below, Applicant requests that the rejections be withdrawn and the claims be allowed to issue.

1. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 5, 9, 20-25 and 27-30 are rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the claims encompass subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, the claims are drawn to a product or method for reducing ß-cell dysfunction in an individual with a pancreatic disorder comprising administering a nucleic acid encoding any IL-1 ß inhibitor, or any inhibitor of

Fas mediated apoptosis; however, a broad genus of inhibitors have not been described in the specification.

Applicants assert that the present invention encompasses methods of reducing ß-cell dysfunction comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1ß or FAS mediated apoptosis into a ß-cell. Applicants disclose a number of different inhibitors of IL-1ß activity including NF-KB inhibitors, STATS, STAT6 and NF-AT, as well as inhibitors of FAS mediated apoptosis. Furthermore, the specification teaches that such inhibitors can be identified by their ability to inhibit insulin release from ß-cells in the presence of IL-1ß and/or their ability to inhibit nitric oxide production in the presence of IL-1ß. Given the teaching of such distinguishing characteristics associated with IL-1ß inhibitors, one skilled in the art could determine whether a given composition functioned as an IL-1ß inhibitor , and was thus, encompassed Claims 1, 5, 9, 20-25 and 27-30.

Claims 20-30 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner maintains that the specification, while being enabling for constructing adenoviral vectors with or without E1 and E3 deletions comprising the (i) IL-1Ra gene with a CMV promoter and (ii) IGF-1 gene with a SV40 promoter and (iii) lentiviral vector comprising the IL-1Ra gene, does not reasonably provide enablement for any recombinant viral vector comprising any sequence encoding an inhibitor of IL-1 ß activity. According to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-12 stand rejected under 35 U.S.C. 112 first paragraph. The Examiner alleges that the claims contain subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or to which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner maintains that the claims are directed to (1) a method for the reduction of ß-cell dysfunction and hence treatment of an individual with pancreatic disease and (2) a method for reducing Fas mediated ß-cell apoptosis in an individual with a pancreatic disease and hence treatment of the same, by the administration of recombinant viral vectors are not enable; however, according to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or to which it is most nearly connected, to use the invention.

Applicants have amended claims 1 and 7 to encompass methods for reducing ß-cell dysfunction and ß-cell apoptosis comprising introducing a nucleic acid molecule encoding either an inhibitor of IL-1ß, or an inhibitor of Fas mediated apoptosis into a ß-cell wherein expression of said nucleic acid molecule results in a reduction in ß-cell dysfunction. Applicants assert that the amended claims are fully enabled by the specification.

In addition, as asserted by Applicants in their previously filed amendment, the requirement for enablement can be found expressly stated in the first paragraph of 35 U.S.C. §112, which requires that the disclosure of an invention be "in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The test for enablement is whether one reasonable skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *U.S. v Telectronics, Inc.* 857 F.2d 778, 8 USPQ2d 1217, (Fed. Cir. 1988).

The present invention is based on the discovery that β-cell dysfunction can be reduced in cells that express an inhibitor of IL-1β or an inhibitor of Fas mediated apoptosis in a β-cell. The instant specification, as filed, discloses (i) specific regulators of IL-1β activity (see, page 15, line 1 through page 16, line 4 of the specification) and inhibitors of FasL triggered apoptosis (see, page 16, lines 5-17 of the specification); (ii) methods for deriving nucleic acid molecules encoding such regulators and inhibitors (see, page 18, line 3 through page 19, line); and (iii) recombinant expression vectors that can be utilized to express such nucleic acid molecules (see, page 19, line 8 through page 23, line 7 of the specification). Further, the specification describes methods for transfer and expression of nucleic acid molecules into pancreatic β-cells (see, page 23, line10 through page 27, line 11 of the specification). Moreover, the working examples of the specification demonstrate the successful transfer of nucleic acid molecules into pancreatic β-cells. Finally, the specification teaches (i) methods for determining effective doses (see, page 28, line 1- 6 of the specification);(ii) *in vivo* methods of administering nucleic acids (see, page 27, lines 14-20 of the specification) and *ex vivo* methods of administering pancreatic cells to a recipient host (see, page 28, line 7 through page 31, line 2 of the specification); and (iii) co-administration of specific immunosuppressive agents to the recipient host to prevent graft rejection (see, page 29, lines 14-19 of the specification).

Applicants maintain that given the specific teachings of the specification, one skilled in the art could, without undue experimentation, practice the claimed methods of the invention. All that is required is that the skilled artisan, follow the teachings of the specification.

In addition, the Examiner is reminded that a patent need not teach, and preferably omits, what is well known in the art. *Lindemann Maschinenefabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984). As set forth in Applicants' previous response, given the teachings of the specification, and general knowledge that is well known in the art concerning, for example, (i) inhibitors of interleukin-1 activity; (ii) viral vectors for use in gene therapy; and (iii) successful transfer and expression of nucleic acids within pancreatic β-cells, one skilled in the art could readily prepare and utilize the claimed vectors without undue experimentation.

Moreover, Applicants content that the present invention is based on the discovery that transfer of nucleic acid molecules encoding inhibitors of IL-1β reduced β-cell dysfunction. Applicants assert that to the extent the Examiner's rejection is based upon the assumption that not all inhibitors of IL-1β will reduce β-cell dysfunction, Applicants respectfully suggest that such a basis is incorrect. The pending claims require that expression of the nucleic acid molecule results in a reduction in β-cell dysfunction. Since the claims are directed to such, they do not read on methods that do not retain this property.

In view of the foregoing remarks, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

2. THE CLAIMS ARE NOT OBVIOUS

Claims 20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (U.S. Pat. No.: 5,977,341; "Monia '341"), in view of

Monia et al. (U.S. Pat. No.: 5,962,673; "Monia "673"), and further in view of Crawford et al. (U.S. 6,107,057; Crawford '057"), and Robbins et al.

The Examiner alleges that claims 20 and 25 are directed to a recombinant retroviral vector comprising a nucleic acid molecule encoding any inhibitor of IL-1 beta activity and specifically an inhibitor of NF-kappa B activity, respectively.

According to the Examiner, Monia '341 teaches that NF-kappa-B normally exists in the cytoplasm bound to a family of inhibitor proteins known as IKB-alpha and IKB-beta. (See col. 1, line 43-49). Although Monia '341 does not teach the nucleotide sequence encoding IKB alpha, Monia '673 teaches nucleic acids encoding inhibitor-kappa B kinase alpha. Monia does not expressly disclose that the IKβ-alpha gene is inserted into a retroviral vector. However, recombinant DNA technology has revolutionized the way genes can be inserted into different vectors and expressed by means of specified promoters. One of ordinary skill in the art would have been motivated to do this as Crawford '057 stated that methods for introducing heterologous polynucleotides into mammalian cells are known in the art and include viral infection.

Thus, the Examiner concludes that one of ordinary skill in the art would have a reasonable expectation of success as methods of construction of a bacterial expression vector is different from that for the construction of mammalian expression vectors etc., all of which are constructed in accordance with techniques well known in the art. Additionally, Robbins et al., in their recent review on viral vectors, have described the construction of retroviral vectors and their efficacy in gene transfer.

Claims 20 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crawford '057, in view of Robbins et al.

The Examiner maintains that claim 26 is directed to a retroviral vector comprising a nucleic acid molecule encoding an inhibitor of IL-1 beta activity wherein the inhibitor is an insulin like growth factor-1 protein (IGF-1). Claim 20 is directed to a retroviral vector comprising a nucleic acid molecule encoding any inhibitor of IL-1 beta activity. Crawford taught a heterologous nucleotide sequence such as IGF-1 gene (insulin like growth factor) cloned into an autonomously replicating vector. Although, Crawford does not expressly disclose that the IGF-1 gene is inserted into a retroviral vector. One of ordinary skill in the art would have been motivated to insert a gene into different vectors and express the gene by means of specified promoters.

The Examiner alleges that one of ordinary skill in the art would have a reasonable expectation of success as methods of construction of a bacterial expression vector is different from that for the construction of mammalian expression vectors, etc., all of which are constructed in accordance with techniques well known in the art. Additionally, Robbins et al. in their recent review on viral vectors, have described the construction of retroviral vectors and their efficacy in gene transfer. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to insert the IGF-1 gene into a retroviral vector.

As set forth in *Graham v. Deere*, a finding of obviousness under 35 U.S.C. 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deer, Inc.*, 383 U.S.I. (1966). The art must provide both the suggestion

of the claimed invention and a reasonable expectation of success. In re *Vaeck*, 947 F.2d 488, 20 USPQ 2d 1348 (Fed. Cir. 1991).

Applicants assert that the claimed vectors are not rendered obvious in view of the cited references because each of the cited references fails to disclose, or even suggest, the fact that expression of an IL-1β inhibitor could reduce β-cell dysfunction. Thus one of ordinary skill in the art would not have been motivated to insert a nucleic acid molecule encoding an IL-1β inhibitor into a retroviral vector for the purpose of reducing β-cell dysfunction. Thus, the invention is not rendered obvious. Applicants respectfully request, therefore, that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

Attached hereto as APPENDIX A is a marked-up version of the changes made to the claims by the current amendment. Entry of the foregoing amendments and remarks into the file history of the above identified application and reconsideration of the claims is respectfully requested.

Applicants believe that the claimed invention is patently distinct from the references cited by the Examiner and that the foregoing amendments and remarks place the claims in condition for allowance. An allowance is earnestly sought.

Respectfully submitted,

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APPENDIX

The claims have been amended as follows:

1. (amended) [A method for reducing ß-cell dysfunction in an individual with a pancreatic disorder, comprising:

(a) introducing a nucleic acid molecule encoding an inhibitor of IL-1ß into a ß-cell ; and

(b) transplanting the ß-cell of step (a) into the idividual so as to reduce ß-cell dysfunction.] A method of reducing ß-cell dysfunction comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1ß into a ß-cell whereby expression of said nucleic acid molecule results in a reduction in ß-cell dysfunction.

5. (amended) [A method for reducing Fas mediated ß-cell apoptosis in an individual with a pancreatic disorder, comprising:

(a) introducing a nucleic acid molecule encoding an inhibitor of Fas mediated ß-cell apoptosis into a ß-cell ; and

(b) transplanting the ß-cell of step (a) into the idividual so as to reduce ß-cell dysfunction.] A method for reducing Fas mediated ß-cell apoptosis comprising introducing a nucleic acid molecule encoding an inhibitor of Fas mediated apoptosis into a ß-cell whereby expression of said nucleic acid molecule results in a reduction in ß-cell dysfunction.